

Multiple valve replacement with pericardial xenograft

Clinical and haemodynamic study

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SUMMARY Multiple valve replacement with pericardial xenografts (sizes 17 to 31) was undertaken in 76 patients. The incidence of early and late deaths was 10.5 and 3.9 per cent, respectively. Actuarially it is predicted that 94.7 ± 3.9 per cent of hospital survivors will be alive at three and a half years after valve replacement. Though long-term anticoagulants were not used, thrombotic valve obstruction was not seen in this series. A systemic embolus occurred early in one case only (0.95 episodes/100 patient years). Mechanical dysfunction of the pericardial xenograft has not been seen.

Haemodynamic studies were performed in seven patients, eight to 21 months after valve replacement. The transvalvular gradients were negligible across the aortic pericardial xenografts. Gradients across mitral and tricuspid xenografts were small. The calculated surface areas ranged from 1.0 to 1.4 cm² for aortic, 1.7 to 2.1 cm² for mitral, and 2.0 to 2.4 cm² for tricuspid valves.

These results after multiple valve replacement are comparable to those reported with isolated mitral or aortic pericardial xenografts over a similar period of observation.

Glutaraldehyde stabilised pericardial xenografts have been used for single valve replacement for more than eight years with very good clinical and haemodynamic results.¹⁻⁶ Since 1976, when the pericardial xenograft became generally available, it has been used for all the valve replacements at our institution. This preliminary report describes the clinical and haemodynamic experience with 76 patients who underwent multiple valve replacement with the Ionescu-Shiley pericardial xenograft.

Patients and methods

Since March 1971, pericardial xenografts have been implanted in 506 patients. Of these, 430 have had single valve replacement (230 aortic, 196 mitral, and 4 tricuspid). Seventy-six patients have had multiple valve replacement, all between April 1976 and September 1979. The present study describes the clinical and haemodynamic follow-up of these 76 patients who received a total of 160 pericardial xenografts (Table 1).

All valves used were manufactured by a standardised process.* There were 25 men and 51 women and the mean age was 50.0 ± 1.4 years (range 26 to 68). The preoperative clinical details of the

patients are shown in Table 2. All valve replacement operations were performed using total body hypo-

Table 1 Number of patients and valves replaced

Valves replaced	No. of patients
Mitral and aortic	54
Mitral and tricuspid	14
Mitral, aortic, and tricuspid	8
Total	76

Table 2 Preoperative clinical details of 76 patients with multiple valve replacement

	Number	Per cent
Men	25	33
Women	51	67
Age (y):		
Mean	50.0 ± 1.4	
Range	26-68	
NYHA class:		
II	5	7
III	54	71
IV	17	22
Rhythm:		
Sinus	20	26*
Atrial fibrillation	56	74
Previous cardiac surgery	26	34
Valve replacement and repair	6	
Closed mitral valvotomy	19	
Mitral and aortic valve replacement	1	

* All patients in sinus rhythm had mitral and aortic valve disease.

* Shiley Laboratories Inc, Irvine, California, USA.

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Table 3 Sizes of pericardial xenografts implanted in 76 patients

Valves	Annulus diameter (mm) of implanted xenografts							Total
	17	19	21	23	25	27	29	
Mitral					16 (2)	40 (4)	17 (1)	76 (7)
Tricuspid						8 (2)	10 (2)	22 (6)
Aortic	3	19 (2)	25 (2)	12	3		4 (2)	62 (4)
Total	3	19	25	12	19	48	27	160

Figures in parentheses represent the number of valves of each type in patients subjected to reinvestigation.

thermia (20 to 26°C) with cold cardioplegia and topical hypothermia. The temperature of the inter-ventricular septum was maintained by these combined measures between 16 and 18°C. The annulus diameter of the pericardial xenografts implanted ranged from 17 to 31 mm (Table 3). Annuloplastic procedures were not performed irrespective of the size of the aortic root. At the time of valve replacement, 39 additional surgical interventions were undertaken in 33 patients, as shown in Table 4.

All patients received oral sodium warfarin from the second or third postoperative day for a period of four to six weeks. The prothrombin time was maintained around or below twice normal. Long-term anticoagulation was not used.

All patients were seen at six-monthly intervals after operation. Seven patients were reinvestigated between eight and 21 months (mean 12 months) post-operatively. Three had had mitral and tricuspid, one mitral and aortic, and three mitral, aortic, and tricuspid valve replacement. The criteria for selection for reinvestigation were the availability of complete preoperative haemodynamic and angiographic data and the informed consent of the patients. The annulus diameters of the pericardial xenografts investigated are shown in Table 3.

Table 4 Additional surgical procedures undertaken at time of valve replacement

Procedure	Number
Aortocoronary saphenous vein bypass graft	11
Tricuspid annuloplasty	7
Resection of hypertrophied left ventricular outflow tract	8
Epicardial pacemaker implantation	3
Closure of atrial septal defect	2
Resection and tailoring of ascending aorta	1
Obliteration of left atrial appendage	2
Decalcification of left atrial wall	1
Removal of left atrial clot	2
Repair of femoral artery aneurysm	1
Repair of lacerated superior vena cava	1
Total procedures	39 (33)*

* Figure in parentheses denotes the number of patients.

Right and left heart catheterisation was performed in the fasting state without prior sedation. All patients with an aortic valve replacement underwent transeptal catheterisation as well. Cardiac output was obtained by the direct Fick method. Both peak and ejection systolic gradients across aortic pericardial xenografts were measured. The ejection systolic gradient was obtained by planimetric integration of simultaneously recorded phasic left ventricular and aortic root tracings. The mean diastolic gradient across mitral and tricuspid xenografts was measured by planimetric integration of simultaneously recorded phasic ventricular and pulmonary wedge or right atrial tracings, respectively. The xenograft surface area was calculated according to the hydraulic formula of Gorlin and Gorlin⁷ using ejection systolic and mean diastolic gradients. Ventricular and/or aortic root angiograms were performed in all patients.

Actuarial analysis for the expected survival rate and for individual event-free curves of reoperation and thromboembolism was carried out using the method of Anderson *et al.*⁸ For the calculation of survival rate hospital deaths were excluded. Standard formulae were used for statistical analysis.

Results

HOSPITAL MORTALITY

There were eight (10.5%) early deaths (within 30 days of the operation) and none of them was related to valve failure. Six patients died from cardiac causes which were: myocardial failure in three instances, ventricular arrhythmia in two, and myocardial infarction in one. The other two deaths were caused by gastrointestinal haemorrhage in one patient and renal failure in another one. Pre-operatively, all these patients were in either New York Heart Association class III or IV.

LATE MORTALITY

There were three (3.9%) late deaths, at three, five, and 12 months after operation. The causes of death were urinary tract infection and Gram-negative

septicaemia, myocardial failure, and cardiac failure after reoperation for bacterial endocarditis.

The actuarial analysis predicts that 94.7 ± 3.9 per cent of hospital survivors will be alive at one and at three and a half years after valve replacement (Fig. 1).

The 65 long-term survivors have been followed for a total of 1257 patient months, with a mean individual follow-up of 19.3 months (range three to 42).

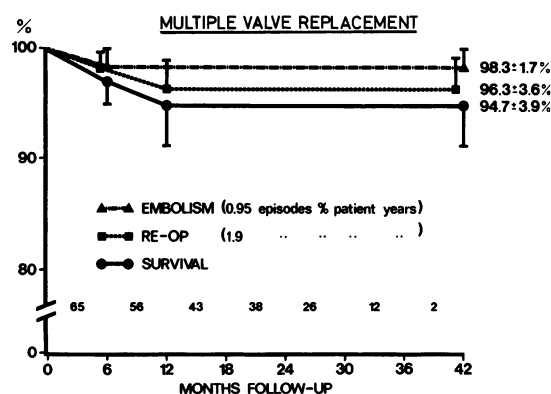


Fig. 1 Actuarial analysis of results after multiple valve replacement with pericardial xenografts. The data are expressed as percentage of expected survival rate and individual event-free curves. The numbers along the horizontal axis denote the number of patients at the beginning of each six-monthly period. Hospital mortality has been excluded from actuarial calculation.

THROMBOEMBOLISM

Long-term anticoagulation was not used. One patient (1.3%) with mitral, aortic, and tricuspid valve replacement developed a transient left hemiparesis on the second postoperative day. Actuarially it is predicted that 98.3 ± 1.7 per cent of patients will be free from embolism at three and a half years after valve replacement (Fig. 1). Thrombotic valve obstruction has not been encountered in this series.

ENDOCARDITIS

Two patients (2.6%) developed endocarditis, at 12 and 20 months after operation. The first patient was reoperated upon and died in the early postoperative period. The second patient, who developed Rickettsial endocarditis, is undergoing long-term medical treatment, which at the time of writing appears to be controlling the disease.

REOPERATION

Three patients (3.9%) underwent reoperation. One had replacement of the infected pericardial valve, as

described above, and two patients had closure of perivalvar (mitral) leak, at five days and 10 months, respectively, after valve insertion. Both these patients are alive and well. 96.3 ± 3.6 per cent of hospital survivors are predicted not to need reoperation at one and at three and a half years after valve replacement (Fig. 1).

CLINICAL DATA

Forty-eight of the 65 long-term survivors had been in New York Heart Association class III and 12 in class IV preoperatively; 5 had been in class II. At the latest postoperative visit 39 were now in class I and the remaining 26 were in class II (Fig. 2).

The preoperative cardiathoracic ratio of the entire group was 62.3 ± 1.22 per cent and it had decreased significantly to 57.5 ± 1.0 per cent ($p < 0.001$) at the latest postoperative visit. On analysis of the three subgroups this high level of significance applied only to those patients with mitral and aortic valve replacement ($p < 0.001$), though the other two subgroups also showed significant reductions in cardiathoracic ratio (Fig. 2).

There were no changes in the proportion of patients with atrial fibrillation (74%) and with sinus rhythm (26%) between the preoperative and the latest postoperative visit. No significant change was noted in either left or right ventricular forces in the electrocardiogram.

HAEMODYNAMIC DATA

The results of the haemodynamic investigations are summarised in Table 5. The cardiac output was normal in patients with either mitral and aortic, or mitral and tricuspid valve replacement, while in

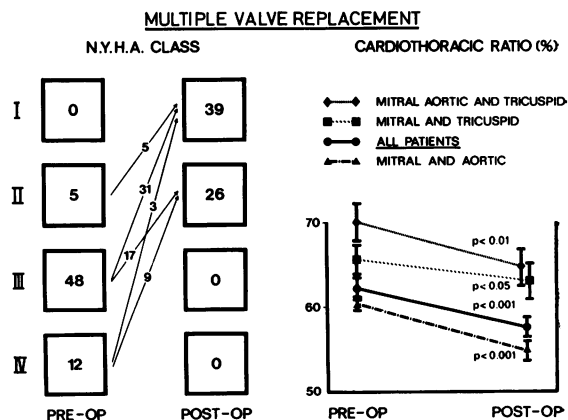


Fig. 2 Diagrammatic representation of pre- and postoperative New York Heart Association class status and cardiathoracic ratio of 65 long-term survivors.

Table 5 Postoperative haemodynamic data (mean values \pm SEM) of seven patients with multiple valve replacement

Valves replaced	No. of patients	CI (l/min per m ²)	RAP (mmHg)	PAP (mmHg)	PWP (mmHg)	LVEDP (mmHg)	Transvalvular gradient (mmHg)			XSA (cm ²)		
							Mitral*	Aortic†	Tricuspid*	Mitral	Aortic	Tricuspid
Mitral and aortic	1	2.7	6	26	17	14	6.4	6.0	—	2.0	1.4	—
Mitral and tricuspid	3	2.6	9.0	28.7	17.4	13.7	6.6	—	2.8	1.9	—	2.2
		± 0.6	± 2.3	± 3.7	± 2.0	± 2.6	± 0.6		± 0.5	± 0.1		± 0.1
Mitral, aortic and tricuspid	3	2.4	10.4	31.2	18.6	15.4	6.2	7.0	3.0	1.9	1.3	2.1
		± 0.2	± 2.3	± 5.0	± 3.0	± 2.4	± 1.4	± 1.0	± 0.6	± 0.2	± 0.2	± 0.1

Abbreviations: SEM, standard error of the mean; CI, cardiac index; RAP, mean right atrial pressure; PAP, mean pulmonary artery pressure; PWP, mean pulmonary wedge pressure; LVEDP, left ventricular end-diastolic pressure; XSA, calculated xenograft surface area. * Mean diastolic gradient. † Peak systolic gradient.

patients with triple valve replacement it failed to reach normal levels. The calculated surface area ranged from 1.0 to 1.4 cm² for aortic, 1.7 to 2.1 cm² for mitral, and 2.0 to 2.4 cm² for tricuspid pericardial xenografts. The transvalvular gradients were negligible across the aortic and small across the mitral and tricuspid valves. At angiography all xenografts were found to be competent.

Discussion

Very encouraging long-term clinical and haemodynamic results after isolated mitral or aortic valve replacement with the pericardial xenograft have already been reported,¹⁻³ but there is no published data concerning the use of the Ionescu-Shiley pericardial xenograft for multiple valve replacement.

The present study has shown very good survival and considerable clinical and haemodynamic improvement in patients with multiple valve replacement up to three and a half years after operation.

The hospital mortality of 10.5 per cent compares favourably with reported data⁹⁻²⁰ and none of the hospital deaths was related to valve failure. All patients who died were in New York Heart Association class III or IV. There were only three late deaths (3.9%) in the present series during the follow-up period and all occurred within 12 months of operation.

Actuarially it is predicted that 94.7 \pm 3.9 per cent of hospital survivors will be alive at one and at three and a half years after valve replacement (Fig. 1). This actuarial survival rate is similar to the figures reported with either mechanical prostheses^{13-16 18 21} or porcine valves^{15 17 20 22} for similar periods of follow-up. Fig. 3 shows, for comparison, the survival curves of patients having isolated aortic or mitral valve replacement with pericardial xenografts. Though the duration of follow-up of patients with multiple valve replacement is shorter,

the survival curve of this group (for the initial three and a half postoperative years) is comparable to the survival of patients with single valve replacement. This observation is at variance with other reports^{18 21 22} which show a lower survival ratio in patients with multiple valve replacement.

Thrombotic valve obstruction, which has been described with mechanical prostheses^{18 23} and porcine valves,^{21 22 24} has not been encountered with the pericardial xenograft, either with single valve, or in the present series of multiple valve replacement, though long-term anticoagulation was not used. The absence of thrombotic obstruction is the more significant in the present series as it includes 22 patients in whom the tricuspid valve has been replaced. Even though 74 per cent of patients were in chronic atrial fibrillation pre- and postoperatively, there was only one transient

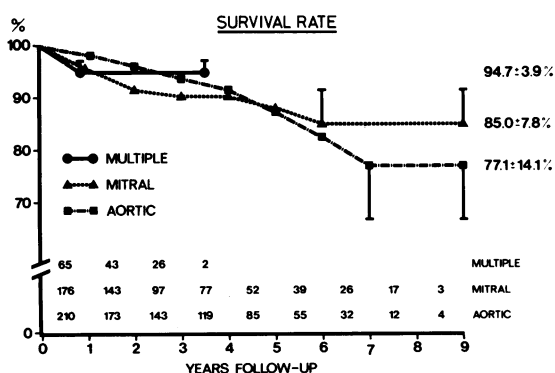


Fig. 3 Actuarial representation of survival rates in patients with multiple valve and single mitral or aortic valve replacement. The continuous line denotes patients with multiple valve replacement. The broken lines show patients with single valve replacement.

embolic event (0.95 episodes/100 patient years) in this series and it occurred on the second post-operative day in a patient with triple valve replacement. Actuarially it is predicted that 98.3 ± 1.7 per cent of our patients with multiple valve replacement will be free from embolism three and a half years after operation (Fig. 1).

The embolic rate in this series is lower than that reported from patients having multiple valve replacement with either mechanical prostheses^{9-14 16 18} or porcine valves.^{17 20 22} This low incidence of embolism is comparable with that encountered in patients having single valve replacement with pericardial xenografts and observed for a similar duration of follow-up, as shown in Fig. 4. It is interesting that the embolic episodes in patients with either single or multiple valve replacement with pericardial xenografts all occurred in the first six postoperative weeks,^{1 3 25} the only exception being a left femoral artery embolus 67 months after isolated mitral valve replacement in one patient.²⁶ The results from this study have reinforced our conviction that long-term anticoagulant treatment in patients with pericardial xenografts is unneces-

sary, the most likely explanation for the absence of thrombotic valve obstruction and for the very low embolic rate being the superior hydraulic characteristics of this valve compared with the porcine valve.^{3 27}

The incidence of endocarditis in this series (1.9 episodes/100 patient years) is similar to that reported with other types of valve replacement.^{12-14 16 20}

All patients derived considerable benefit from the operation, 60 per cent being in New York Heart Association class I and 40 per cent in class II at the most recent follow-up.

The haemodynamic investigations performed in seven patients at a mean of 12 months after operation showed normal cardiac outputs at rest. The pulmonary wedge and left ventricular end-diastolic pressures did not return to normal levels, which is not unexpected as all these patients had been in New York Heart Association class III and IV preoperatively. Similar observations have been made by others.^{15 19 21} The peak systolic and mean diastolic gradients across the aortic and atrioventricular valves were similar to those which have been obtained in patients with isolated aortic or mitral valve replacement with pericardial xenografts.⁴⁻⁶ The calculated surface areas of the aortic pericardial xenografts were 1 cm² or larger. Thus complicated annuloplastic procedures are unnecessary in patients with a small aortic annulus because of the optimal ratio of implantation diameter to orifice area of the pericardial xenograft valve. The mitral and tricuspid xenografts had areas around 2 cm². These data from a small number of patients having multiple valve replacement are similar to those obtained in a larger series of patients with isolated aortic or mitral valve replacement with pericardial xenografts.^{5 6} For this reason catheterisation of a larger number of patients with multiple replacements was not considered at this stage.

Table 6 summarises the incidence of major complications in our entire experience with 590 pericardial xenografts inserted in 506 patients. Mechanical dysfunction of the pericardial xenograft

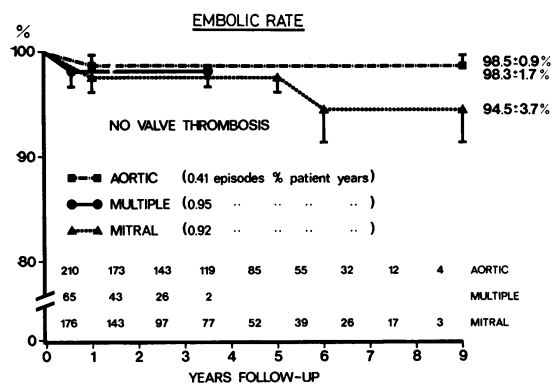


Fig. 4 Actuarial representation of event-free curves for embolism in patients with multiple valve and single mitral or aortic valve replacement.

Table 6 Incidence of significant complications in patients with pericardial xenografts

Valves replaced	No. of patients	Years of follow-up	Episodes per 100 patient years			
			Endocarditis	Perivalve leak	Embolism	Valve dysfunction
Aortic	230	730	0.55	0.69	0.41	0.96
Mitral	196	542	0.92	0.74	0.92	0.92
Tricuspid	4	22	—	—	—	—
Multiple	76	105	1.9	1.9	0.95	—
Total	506	1399	0.79	0.79	0.64	0.86

has not been observed in either this multiple replacement series or the single replacement series using pericardial xenografts manufactured commercially^{3 25} and implanted since April 1976.

In conclusion, this preliminary study of patients with multiple valve replacement has shown a very low propensity for embolism in the absence of long-term anticoagulation and superior haemodynamic performance of the pericardial xenograft when compared with other tissue valves.^{15 20} Continuous, systematic follow-up of patients with pericardial xenografts will provide the necessary data on progressively longer periods of observation.

References

- Ionescu MI, Tandon AP, Mary DAS, Abid A. Heart valve replacement with the Ionescu-Shiley pericardial xenograft. *J Thorac Cardiovasc Surg* 1977; **73**: 31-42.
- Ionescu MI, Tandon AP. Long-term clinical and haemodynamic evaluation of the Ionescu-Shiley pericardial xenograft heart valve. *Thoraxchir Vask Chir* 1978; **26**: 250-8.
- Ionescu MI, Tandon AP. The Ionescu-Shiley pericardial xenograft heart valve. In: Ionescu MI, ed. *Tissue heart valves*. London: Butterworths, 1979: 201-52.
- Tandon AP, Smith DR, Mary DAS, Ionescu MI. Sequential haemodynamic studies in patients having aortic valve replacement with the Ionescu-Shiley pericardial xenograft. *Ann Thorac Surg* 1977; **24**: 149-55.
- Tandon AP, Smith DR, Whitaker W, Ionescu MI. Long term haemodynamic evaluation of aortic pericardial xenograft. *Br Heart J* 1978; **40**: 602-7.
- Tandon AP, Smith DR, Ionescu MI. Hemodynamic evaluation of the Ionescu-Shiley pericardial xenograft in the mitral position. *Am Heart J* 1978; **95**: 595-601.
- Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am Heart J* 1951; **41**: 1-29.
- Anderson RP, Bonchek LI, Grunkemeier GL, Lambert LE, Starr A. The analysis and presentation of surgical results by actuarial methods. *J Surg Res* 1974; **16**: 224-30.
- Bigelow JC, Herr RH, Wood JA, Starr A. Multiple valve replacement. Review of five years' experience. *Circulation* 1968; **38**: 656-63.
- Midell AI, DeBoer A. Multiple valve replacement. An analysis of early and late results. *Arch Surg* 1972; **104**: 471-6.
- Pluth JR, Broadbent JC, Barnhorst DA, Danielson GK. Aortic and mitral valve replacement with cloth-covered Braunwald-Cutter prosthesis. *Ann Thorac Surg* 1975; **20**: 239-48.
- Stephenson LW, Kouchoukos NT, Kirklin JW, Karp RB, Pacifico AD. Combined aortic and mitral valve replacement: results in 251 patients (abstract). *Circulation* 1975; **51** & **52**, suppl II: 31.
- Åberg B, Henze A, Björk WO. Combined aortic and mitral valve replacement with the Björk-Shiley tilting disc valve prosthesis. *Scand J Thorac Cardiovasc Surg* 1977; **11**: 1-10.
- Lepley D Jr, Flemma RJ, Mullen DC, Singh H, Chakravarty S. Late evaluation of patients undergoing valve replacement with the Björk-Shiley prosthesis. *Ann Thorac Surg* 1977; **24**: 131-9.
- Rhodes GR, McIntosh CL, Redwood DR, Itscoitz SB, Epstein SE. Clinical and hemodynamic results following triple valve replacement: mechanical vs porcine xenograft prostheses. *Circulation* 1977; **56**, suppl II: 122-7.
- Stephenson LW, Kouchoukos NT, Kirklin JW. Triple-valve replacement: an analysis of eight years' experience. *Ann Thorac Surg* 1977; **23**: 327-32.
- Stinson EB, Griep RB, Oyer PE, Shumway NE. Long-term experience with porcine aortic valve xenografts. *J Thorac Cardiovasc Surg* 1977; **73**: 54-63.
- Björk VO, Henze A. Prosthetic heart valve replacement. Nine years experience with the Björk-Shiley tilting disc valve. In: Ionescu MI, ed. *Tissue heart valves*. London: Butterworths, 1979: 1-28.
- Nitter-Hague S, Frøysaker T, Enge I, Rostad H. Clinical and haemodynamic observations after combined aortic and mitral valve replacement with the Björk-Shiley tilting disc valve prosthesis. *Scand J Thorac Cardiovasc Surg* 1979; **13**: 25-31.
- Oyer PE, Stinson EB, Rossiter SJ, Miller DC, Reitz BA, Shumway NE. Extended experience with the Hancock xenograft bioprosthesis. In: Sebening F, Klövekorn WP, Meisner H, Struck E, eds. *Bioprosthetic cardiac valves*. Munich: Deutsches Herzzentrum München, 1979: 47-59.
- Melvin DB, Tecklenberg PL, Hollingsworth JF, et al. Computer-based analysis of preoperative and postoperative prognostic factors in 100 patients with combined aortic and mitral valve replacement. *Circulation* 1973; **47** & **48**, suppl III: 56-62.
- Cohn LH, Collins JJ Jr. The glutaraldehyde stabilized porcine xenograft valve. In: Ionescu MI, ed. *Tissue Heart valves*. London: Butterworths, 1979: 173-200.
- Bonchek LI, Starr A. Ball-valve prostheses: current appraisal of late results. *Am J Cardiol* 1975; **35**: 843-54.
- Johnson AD, Daily PO, Peterson KL, et al. Functional evaluation of the porcine heterograft in the mitral position. *Circulation* 1975; **52**, suppl I: 40-8.
- Ionescu MI, Tandon AP. Long-term clinical and haemodynamic evaluation of the Ionescu-Shiley pericardial xenograft heart valve. In: Sebening F, Klövekorn WP, Meisner H, Struck E, eds. *Bioprosthetic cardiac valves*. Munich: Deutsches Herzzentrum München, 1979: 199-213.
- Ionescu MI, Whitaker W, Tandon AP. Mitral valve replacement without long-term anticoagulants (8.5 years experience with pericardial xenograft) (abstract). *Br Heart J* 1980; **43**: 118.

- 27 Gabbay S, McQueen D, Yellin EL, Frater RWM. In vitro hydrodynamic comparison of mitral valve prostheses at high flow rates. *J Thorac Cardiovasc Surg* 1978; **76**: 771-87.

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